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| 10/681,418 | 10/07/2003 | H. Michael Shepard | NB 2008.01 | 7416 |

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BINGHAM, MCCUTCHEN LLP
THREE EMBARCADERO CENTER
18 FLOOR
SAN FRANCISCO, CA 94111-4067

| EXAMINER | |
|---|---|
| CRANE, LAWRENCE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/681,418 | SHEPARD ET AL. | |
| | Examiner | Art Unit | |
| | L. E. Crane | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09/20 & 11/15/2004 (amdts)*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *53-61 and 63-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-61 and 63-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim **62** has been cancelled, claims **53-59, 65, 71-74, 77-78, 80-82** have been amended, the disclosure has been amended, and no new claims have been added as per two amendments filed September 20 and November 15, 2004. Two Information Disclosure Statements (2 IDSs) both filed August 9, 2004 have been received with all but two of the cited references.

Claims **53-61 and 63-93** remain in the case.

Examiner notes the submission of 103 additional references (115 total less 10 duplicate cites) in the two IDSs (7 and 19 pages, respectively) filed August 9, 2004. Examiner has obtained copies of all 103 non-duplicate references. Examiner has reviewed all of said references, but has reviewed the first 55 cited (refs. 16, 61, 164-169, 171-172, 174-183, 185-190, 192-196, 198-204, and 206-222; >50% of total new cites) in detail, and has found i) that 40 references are entirely irrelevant to the instant prosecution (no relevance to the claims, general interest only), and that ii) 15 of said references are only tangentially related (mention is made of inhibition of thymidylate synthase or of a nucleoside compound with a few structural features in common with the claimed subject matter).

Examiner has found that no reference or any portion thereof among the first 55 reviewed provides any reasonable basis to amend the rejections of record in any way. For example, there are three particular references among the first 55 citations which examiner has found to have no relevance whatsoever. There reference are a) the chemical applications of "Lawesson's reagent" (ref. 178), b) the isolation of DNA sequences in multidrug resistant hamster cells (ref. 203), and c) the pharmaceutical activity of phosphorylated "Fialuridine" (ref. 212). Analysis of the remaining 48 references supplied (2 are mi

ssing) suggests that only references 229, 239, 253 and 265 are at best tangentially related and that NONE of the the 48 remaining references (non-duplicates between references 223 and 275) would provide any basis for amendment of any rejection of record.

Examiner refers applicant to *Penn Yan Boats v. Sea Lark Boats* (354 F. Supp 948, 175 USPQ 260 (S.D. Fla. 1972) in light of what appears to be an excessive disclosure of superfluous information which may or may not have been made to hide the one reference which examiner has not yet recognized as relevant.

To assist in this matter, examiner respectfully requests applicant to supply a reason why each and every one of the above specifically noted-by-citation-number references have been submitted for consideration; i.e. how the chemical applications of Lawesson's Reagent is relevant to the instant prosecution of compound claims, pharmaceutical composition claims, and related method of treatment claims. This request is being made under the provisions of 37 C.F.R. §1.105.

The disclosure is objected to because of the following informalities:

In the disclosure at page 56, the title at lines 2-3 is missing the letter "o" in five separate locations.

The structures identified at pages 43 and 44 as being either propargylic or allylic moieties are misleading because the three structures shown with substituent formulas specify $C_3H_2$ (propargylic or allenic(?)), but not $C_3H_5$ (allylic).

Appropriate correction is required.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

The error at page 56 is plainly evident on the scanned image but may not be on your original copy (artifact introduced by the scanning process??). Examiner suggests an amendment to correct the flaw in order to avoid a necessary correction later.

The structures at pages 43 and 44 are inconsistent with the printed notations under same. Correction of the structures is again respectfully requested wherein both allylic and propargylic alternatives are both clearly illustrated in the structures (the present structures may be interpreted to be 5-allenylpyrimidines).

Examiner also suggests that the amendments previously made to claim **58** need to be made to claim **86**.

Claims **53, 59-61, 63-72, 75-78 and 85-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims extends to compounds the synthesis of which has not been defined in a manner permitting one of ordinary skill to know the identity of the compounds which have shown activity in the treatment of neoplastic disease conditions. In addition, the claim **63** identifies compounds the synthesis and biological testing of which has not been disclosed, including
i) wherein "$R^1$ is Cl, I or CN,"
ii) wherein "$R^7$ is a ... phosphodiester group or a phosphoramidite group," and
iii) "wherein the compound may be in any enantiomeric, diastereoisomeric or stereoisomeric form, including ... L-form, α-anomeric form."
In addition, applicant has not supplied any data to support the extension of treatments to include "liver cancer."

B. The nature of the invention is directed to 5-substituted-2'-deoxyuridines and analogues thereof as defined by claim **63**, pharmaceutical compositions thereof, a method of testing for relative antineoplastic activity, and method of treating several different neoplastic disease conditions.

C. The state of the prior art is well established by the extensive lists of prior art patents and other references disclosed by the patents issued to Shepard and Shepard et al. listed on the instant PTO-892.

D. The level of one or ordinary skill is high because the practice of the invention requires knowledge of both the organic synthesis of nucleoside analogues and the medical knowledge and training required to properly administer and monitor antineoplastic agents to a host in need thereof.

E. The level of predictability in the art is limited because the number of compounds actually synthesized and/or tested, and the specific disease conditions tested, is very small when compared with the number of compounds included within the scope of the instant claims. In view of the lack complete test data, it is also unclear that the substitution of "Cl," "I" or

particularly the pseudohalogen "CN" for "Br" as an X-substituent will produce equivalent biological testing results. Similarly, most of the variations provided for by the alternatives within the definitions of variables $R^6$ and $R^7$ have neither been synthesized nor tested for biological activity. And, only three neoplastic cell types have been shown to be effectively inhibited. For this reason examiner concludes that the asserted and claimed extrapolation to the effective treatment of all "pathological" cell types is not predictable and therefore not adequately enabled.

F. The amount of direction provided by the inventor is difficult to determine because of incomplete synthetic information and incomplete identifying information concerning the identity of compounds tested for biological activity at page 68. Applicant has not provided enabling support for the synthesis of "any enantiomeric, diastereomeric or stereoisomeric form," and in particular has not shown how to make the L-forms and the α-anomers of any of the claimed compounds, or shown that the asserted and claimed pharmaceutical activity or testing for said activity of claims **59-61 and 87-93** extends to all possible enantiomers and diastereomers of the compounds defined by claims **53 and 63**.

G. The existence of working examples is difficult to determine because of incomplete identifying information concerning either the synthesis of many of the compounds claimed or the identity of compounds tested for biological activity at page 68.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in light of the very limited biological test results and synthetic instructions provided for the compounds defined by claims **53 and 63**. In particular, the instant method of treatment claims are only enabled for the treatment of one variety of breast cancer, one variety of colon carcinoma, and one fibrosarcoma (HT 1080; organ apparently not specified in the disclosure) according to the table at page 68. There are no enabling examples for the claimed method of testing. Therefore, examiner concludes that the amount of experimentation required to practice all aspects of the instant claimed invention is undue.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant argues that " .. the Office has failed to establish a *prima facie* case that the specification does not enable the full scope of the claims" further arguing that "[b]y law a patent application is presumptively enabled when filed" and that PTO must " .. explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence ... ." Examiner notes that applicant's arguments have failed to address the particulars of the rejection of record. In addition examiner notes that in claim **59** the term "method of inhibiting the proliferation of a pathological cell *in vitro,*" and in claim **91** which extends treatment to all *in vivo* applications, cover every possible disease condition including HIV, the common cold, Ebola/Marburg viral infections, and pancreatic cancer *in vitro* or *in vivo*, but that applicant's disclosure fails to provide the very large quantity of specific test data which would adequately support a grant of such all encompassing claim language. Applicant is referred to *Ex parte Balzarini,* 21 USPQ 2d 1892 (Bd Pat App & Inter, 1992) for guidance regarding the enhanced enablement needed to support claims directed to methods of treating HIV (cited in the MPEP at §2107.03(III)). Because this is a case wherein compounds are being claimed to have pharmaceutical efficacy, see MPEP §2164.06 (b)(III) which refers back to MPEP §§2107-2107.03 for the proper standard. The MPEP at §2107.03(III) states as follows: " ... the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility." Examiner finds a clear insufficiency of medical testing data and therefore cannot agree with the requested extrapolation of the instant test data in support of the treatment of HIV *in vitro* or *in vivo*, or to any other of the vast array of disease conditions encompassed by the generic term "pathological cell." Examiner also fails to find sufficient data to support the method of testing (claims **87-90**) the practice of which would appear to be limited to the three neoplastic disease cells only because of the limited known pharmaceutical activity of the compounds of claim **63**. For these reasons the instant grounds of rejection have been maintained.

Claim **63** is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **63** the terms "phosphodiester group" and "phosphoramidate group" are indefinite because each fails to be defined in sufficient detail to permit the ordinary practitioner to determine the structural metes and bounds of the claimed subject matter.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant has noted the above grounds of rejection, but has failed to provide any amendment to correct the obvious problems. For example, a "phosphodiester group" must have two P-O-C linkages, only one if which has been defined herein (what group(s) are present to fill the role of the second ester type substituent?). Phosphoramidate groups may be bound through O or N and the amidate N-portion may be further substituted, variations which have not been specifically addressed in the instant claim. The absence of completely specified definitions of the noted terms continue to render the metes and bound of the claim indefinite.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. §101 which states that "whoever invents of discovers any new and useful process ... may obtain a patent therefor ... ." (emphasis added) Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.,* 151 U.S. 186 (1894); *In re Ockert,* 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. §101) double patenting rejection can be overcome by cancelling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. §101.

Claims **55 and 56** are rejected under 35 U.S.C. §101 as claiming the same invention as that of claims **3 and 4** of prior U.S. Patent No. **6,683,061** (PTO-892 ref. **AB**). This is a double patenting rejection.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant has acknowledged this grounds of rejection but has failed to respond in particular except to indicate that no response will be made until allowable subject matter has been indicated.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy

reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **53-54, 57-61, 63-86 and 91-93** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-2 and 5-10** of U.S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant has acknowledged this grounds of rejection but has failed to respond in particular except to indicate that no response will be made until allowable subject matter has been indicated.

Claims **53-61, 63-86 and 91-93** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-6 and 28-30** of copending Application Serial No. **10/119,927**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant has acknowledged this grounds of rejection but has failed to respond in particular except to indicate that no response will be made until allowable subject matter has been indicated.

Claims **53-86 and 91-93** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **56, 57 and 61** of copending Application Serial No. **09/782,721**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed September 20 and November 15, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant has acknowledged this grounds of rejection but has failed to respond in particular except to indicate that no response will be made until allowable subject matter has been indicated.

Some or all of claims **53-61, 63-86 and 91-93** of this application conflict with claims **1-6 and 28-30** of copending Application Serial No. **10/119,927**, and claims **56, 57 and 61** of copending Application Serial No. **09/782,721**. 37 C.F.R. §1.78(b) provides that where two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

Claims **87-90** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. §112.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX directly to Examiner's computer is 571-273-0651. Telephone number for filing documents officially with the USPTO is **703-873-9306**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
**03/08/2005**

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600